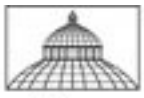

Man and Plants Against Pain[1]

NORMAN GROVER[2]

Our earliest known records refer to banal occurrences: taxes, sports, weather, illness. A disproportionate number of these manuscripts refer to illness and pain. Ignorant though they seem now to have been, ancient peoples occasionally stumbled upon ways to allay pain—and it was often recorded. Nearly all effective pain-relievers discovered by man up to the beginning of the 20th century were of botanical origin. Today, the synthetic analgesics and anesthetics have markedly decreased the importance of botanical preparations, but some remain of unchallenged superiority. This article describes some of these plants and products of past and present importance in combatting pain and attempts to indicate where research may reward us with new botanical analgesics.

Alcohol

The use of alcoholic beverages has paralleled the history of mankind. Alcohol has found a place in social life, religious rites and medical practice. Despite its ancient history and near universal usage, alcohol is rarely a naturally occurring plant product; rather, it is obtained by fermentation, the transformation of sugar into alcohol by various yeasts. Thus, the production of alcohol always involves two plant species: the sugar-containing species and the yeast. Since malting converts starch to sugar, an even larger number of plants is thereby available for the production of alcohol.

Medicinally, alcohol has had many and varied uses, nearly all of them having passed out of favor. Among these was the taking of liquor for anesthesia. When this practice arose is unknown; all evidence seems to indicate that drinking alcohol to excess (to produce anesthesia) is as old as the practice of drinking itself. Likewise, no one geographical region can be pointed out as the original home of the custom. Starch- and sugar-containing species are so widely scattered taxonomically and geographically that the consumption of alcoholic beverages must have arisen independently in sundry parts of the world. The colloquial usage of the expression "to feel no pain" as a synonym for "to be intoxicated" is evidence that contemporary society is well acquainted with the anesthetic effects of alcohol; and current anthropological literature makes it quite evident that primitive societies are equally cognizant of it. The scarcity of documented accounts of primitive "medicine men" using alcohol to relieve the pain of surgery may attest not to their unawareness of alcohol's anesthetic properties but to the backwardness of primitive surgery.

Depending on the quantity ingested, alcohol acts first as an excitant, then as a sedative, hypnotic, analgesic and anesthetic. The effect of alcohol is, therefore, similar to that of ether and other anesthetics now in wide usage. The question then arises: Why has the use of alcohol as an anesthetic been abandoned? Like many of the other general anesthetics, alcohol is a poison if ingested in large quantities, and there is but slight difference between an anesthetic and a lethal dose of alcohol. Alcohol also takes an inconveniently long time before producing anesthesia, and, once an unconscious state has been reached, the patient may be on the verge of respiratory collapse and death. Ether, on the other hand, produces unconsciousness long before a lethal amount is approached. Alcohol has, consequently, been largely abandoned in medicine; but in the absence of competent medical aid, alcohol still remains a widely used home remedy for the alleviation of pain, until professional medical help can be procured.

The Mandrake

The mandrake, or mandragora, *Mandragora officinarum* (Solanaceae) has also been

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dropped from medical use, notwithstanding its proven pain-relieving properties. The derivation of the name is in doubt; some believe that it is derived from the Sanskrit "mandros" (sleep) and "agora" (substance); others hold it to be due to the resemblance of the forked root to male genitalia (whence mandrake). The ancients also had "womandrakes" as common as mandrakes.

The early literature of the Mediterranean area (where the mandrake is native) abounds in references to the "mystical" properties of the little plant. One of the earliest recorded references occurs in Genesis XXX. Rachel ate mandrakes found by Reuben, and they supposedly aided her in conceiving Joseph. The Egyptians, Assyrians, and Persians all have left records of "male plants," used usually as aphrodisiacs; but there is sharp disagreement whether or not these plants were actually *Mandragora officinarum*. The Greeks were undeniably aware of the narcotic properties of this species and apparently employed it as an intoxicant more than for magical purposes. Hippocrates asserted that "a small dose in wine, less than would occasion delirium, will relieve the deepest depression and anxiety." But even if the Greeks were amongst the first to use the plant for legitimate purposes, they also added to the aura of mystery surrounding it; for Theophrastus, in his "History of Plants" (about 230 B.C.), first mentioned the rites and ceremonies associated with gathering the mandrake.

The Romans inherited both the glory and the superstitions of the Greeks. Pliny translated the Greek herbals into Latin, adding some embellishments of his own. By Pliny's time, it was extremely hazardous business to gain possession of a mandrake. One had to stand with his back to the wind, draw three mystic circles about the plant with the point of a sword, turn toward the west, and then, and only then, could one safely dig up the man-plant.

By medieval times, the danger of uprooting a mandrake had become even more extreme. The herb had by then acquired the power of speech, and as it was torn from the ground, it emitted such terrible shrieks that it immediately turned the collector into a madman. But, just as the mind can conceive such horrors, so can it conceive a method of overcoming them. The scheme: the earth about the mandrake was loosened, and the collector then placed wax in his ears. Immediately thereafter, the collector fastened a dog's tail to the plant and offered the dog a piece of bread. In rapid succession, the dog jumped, the mandrake screamed and was torn loose, and the dog died.

Fortunately, however, the use of mandrake as a pain reliever arose and flourished along with this superstition. Dioscorides first mentioned the use of mandrake as an anesthetic, recommending the "wine of mandrake to be given to such as shall be cut or cauterized." By the 6th century, this use of the mandrake was relatively well known. Isidorus wrote: "Its bark is given in wine to those who are about to be surgically operated upon, that they may fall into a stupor and may not feel the pain." And Serapion, writing in the 9th century, stated: "A measure of four obols is given to drink to a person when it is necessary to cauterize or cut. He will not feel the cauterizing or cutting because of the stupor which ensues."

Mandrake continued to be employed as an anesthetic to the 16th century, when writers of the great herbals began to deride the old traditions. Two reasons, both apparently valid, account for the little notice given the drug from that time to the late 19th century. First, better pain relievers were becoming available; secondly, the plant was so thoroughly linked to superstition that medicine, surgery, and pharmacy simply abandoned it in their quest for respectability.

In 1888, B. W. Richardson undertook the first modern investigations of the chemical substances in the plant and, in 1889, Ahrens isolated the alkaloid "mandragorine" from the root. Twelve years later, mandragorine was shown to be a mixture of hyoscyamine and hyoscine (scopolamine) with several other alkaloids. These constituents are the same as those from *Atropa Belladonna, Hyoscyamus niger,* and *Datura Stramonium* which today are so important in medicine. The mandrake has fallen into disuse because of these more readily available sources of its alkaloids.

The Opium Poppy

The opium poppy has been utilized by man from very early times. There are sev-

eral varieties of *Papaver somniferum* (Papaveraceae), one of which (var. *setigerum*) still grows wild in the countries bordering the northern coast of the Mediterranean—though it is by no means certain that the plant originated there. The centers of cultivation are, however, Asia Minor and the Far East, Turkey being the chief supplier of medicinal opium. Other countries figure prominently in opium production as well: Bulgaria, Yugoslavia, Iran, India, China.

Nearly all parts of the plant contain a white milky latex from which the alkaloids are isolated; by far the greatest concentration of latex occurs in the capsules. Inasmuch as the quantity of latex decreases as the fruit matures, collection is initiated usually before the fruit ripens. The collection procedure varies from place to place, but the general technique is more or less constant.

In the early morning or late afternoon when the temperature is low, collectors, with special knives, make several incisions in each capsule, taking care not to cut through the inner wall, in order not to injure the seeds or lose any of the latex. The latex exudes from the severed latex vessels to form brownish cakes which are then taken to a central collecting area and kneaded by hand into a uniform consistency. The hardened latex is then wrapped in leaves and dried in the sun before shipment to commercial buyers.

According to the earliest records, the latex was used to induce analgesia. In this procedure, there lay great danger. We know now that individual reaction to drugs varies; compounded with this was the variation of alkaloid concentration from plant to plant and consequently from one unit of latex to another. The early medical practitioner quickly learned that a given amount of latex might not relieve pain in one case, whereas in another it might well cause deep coma, or even death.

The Ebers Papyrus contains a reference to the opium poppy, but apparently there is no reason to believe that the Egyptians used opium to relieve pain in surgery. The Greeks knew of opium at least as early as 400 B.C., but they used it sparingly. Opium was one of the constituents in Theodoric's "narcotic sponge" of the 13th century, but it was not until the 16th century, when Paracelsus invented laudanum, that the "modern" history of opium really began. Paracelsus' laudanum contained such expensive ingredients as gold and pearls, as well as opium. Laudanum is still in use, but the term is applied only to a tincture of opium.

In 1806, T. W. Sertürner isolated the active ingredient of opium latex. He had tried repeatedly to crystallize the principal, to no avail. One day, after pouring liquid ammonia over the opium, he noticed crystals that he had never seen before. Assuming that these crystals represented the active ingredient, Sertürner was faced with the problem of finding "guinea pigs." First he salted cheese with the crystals and observed the effect on mice. They died. Then he used dogs. Putting the crystals this time into bones, he found that the crystals "made the dogs happy." The time was near for experiments on human beings. He took the crystals himself and had his coterie of friends assist. Sertürner was unconscious for ten hours, having taken twice the amount that is now considered a maximum dose. In fact, however, Sertürner was driven out of his home town of Inbeck as a "quack" and a fraud; but he had succeeded in isolating morphine.

In addition to morphine, the opium poppy contains more than 25 other alkaloids, including codeine which acts more effectively on the "cough center" but less effectively on that area of the brain that senses pain. Morphine itself has virtually no local action; it is not absorbed through the skin, and so its use as a dusting powder is impractical. Although rapidly absorbed through the mucous membranes, it is commonly given by injection. Precisely how morphine acts on the brain is not yet known, though it has been hypothesized that it disrupts "association areas." From subjective reports, we know that mild doses do not abolish pain; the pain is felt but not appreciated. Thus, morphine disrupts the process of assigning affect to pain. Increased doses produce unconsciousness and, consequently, complete relief from pain.

Without a doubt, morphine is today the most widely used analgesic of botanical origin. In cases of accidental trauma (except in

skull fractures or certain internal injuries, where it may mask symptoms) morphine is *the* universally accepted pain-reliever. In addition to its use in accidents, morphine is employed as a pre-operative and post-operative sedative. First tried for this purpose as early as 1850, it did not come into general use until the early 20th century. In 1899, morphine was tried in combination with scopolamine to induce "twilight sleep" for surgery and childbirth. Today, the gaseous anesthetics have replaced morphine for surgical anesthesia, except in certain "poor risk cases" where the side effects of morphine are preferable to those of ether, cyclopropane and the like.

Drugs of the Belladonna Series

The "belladonna series" is a group of drugs—all with similar physiological action—from a group of botanically closely related genera of the Solanaceae. The plants of principal importance are *Atropa Belladonna, Datura meteloides, Datura Stramonium, and Hyoscyamus niger.* Each of these plants had, of course, its own long and unique history, until chemistry and pharmacy united their stories in the field of medical therapeutics.

Belladonna is probably the most familiar name in the list, although there is really no single drug by that name. Like so many other solanaceous plants, *Atropa Belladonna* contains many alkaloids: mostly atropine, hyoscyamine, apoatropine, and belladonnine. *Atropa Belladonna* is native to central and southern Europe and Asia Minor. "Atropa" is derived from the name of the Greek Fate, Atropos, "The Unalterable," who cut the thread of life. The toxicity of the berries may have given rise to this epithet, as well as to our common name "deadly nightshade." The name "belladonna" is of later origin. Matthiolus was the first to use "belladonna," meaning in Italian "beautiful lady," in reference to the use of the plant by Italian ladies of the Middle Ages to induce mydriasis and enhance their beauty. Today, this mydriatic property of atropine is valuable in ophthalmology. The plant was known both to Dioscorides and Theophrastus, but it was not until the 18th century that the alkaloids of *Atropa Belladonna* were employed extensively. The first "modern" reference to *Atropa* alkaloids occurred apparently in the *Pharmacopoeia Wurtembergica* (1st ed., 1764), in which the use of hydrobromide of scopolamine is recommended as a sedative.

The highest concentration of atropine is found in the metabolically most active cells. The roots would, therefore, give a better yield than the leaves; but apparently the producers prefer to obtain more than one harvest from each plant, and, therefore, leave the roots undisturbed. The precursors of atropine are produced in the roots and carried to all other parts of the plant. Rowson (69) showed this by grafting belladonna stems to tomato roots and making the reciprocal graft of tomato stems to belladonna roots. At maturity, he found alkaloids in the belladonna root-tomato stem plants only. The experimental technique was further corroborated in a series of belladonna-potato grafts. Atropine, peculiarly enough, does not occur in nature under normal conditions. What does occur is laevo-hyoscyamine, which, under chemical control, is racemized to atropine.

Atropine has both a central and a local action and is often used consequently as a component of "muscle plasters." It is absorbed through the skin and paralyzes the ends of the pain-conducting nerves. Atropine is likewise readily absorbed into the blood, which carries it throughout the body. Inasmuch as atropine acts on the ends of nearly all the secretory nerves, a local application of atropine may well cause undesirable side effects in areas quite distant from the site of application: arrest of salivation and sweating; cessation of gastric juice and milk production; blurred vision; tachycardia.

When taken internally, atropine acts directly upon the cerebrum, causing initial excitement followed by a prolonged state of sleepiness. It can, therefore, be used as a substitute for morphine, but morphine is the usual choice, since it does not cause initial excitement.

Datura is a widespread genus that has been and still is used on all the continents except Australia for its narcotic properties. *Datura Stramonium,* native prorably to the

region about the Caspian Sea, yields the drug stramonium. Known as early as 37 A.D., it is still a favorite source of "knock-out drops" in the tropics. The name "stramonium" comes apparently from the French "stramoine" meaning stinkweed. The settlers at Jamestown, Virginia, apparently introduced the plant into the New World and attempted to use it as a "pot herb" with nearly fatal results. Thus arose the American name for the plant "Jamestown (Jimson) Weed." It yields atropine and can, therefore, substitute for *Atropa Belladonna* as a source of this alkaloid.

Datura meteloides, of American origin, has been used in Mexico and the American Southwest since earliest times as part of religious and magical rites. Ethnobotanical literature states that the Zuñi Indians of New Mexico used *D. Stramonium* as an anesthetic in breast operations (79) and that the Pueblo used it in heroic doses for surgery (29). Inasmuch as *D. Stramonium* is probably of Old World origin, these accounts may actually refer to *D. meteloides.* On the other hand, J. F. Dastur (22) reports the use of the American *D. meteloides* by the natives of India and Pakistan. These confused reports may possibly be due to the fact that the natives (and botanical writers on occasion) often do not distinguish between species of *Datura.*

The last plant of the series is *Hyoscyamus niger.* Its common names "henbane" and "mort aux poule" are derived from its supposed use by criminals to kill fowl. The earliest reference (2250 B.C.) to *Hyoscyamus* occurs on a Babylonian clay tablet, where the seeds (with gum mastic cement) are recommended for pain of dental caries. Dioscorides recommended its use in poultices, and through the centuries henbane has had periods of use followed by disuse. To obtain its alkaloidal constituents, atropine, hyoscyamine, and scopolamine, henbane leaves are gathered when the plant is in full flower and then carefully dried.

Interestingly enough, the history of scopolamine, one of the chief constituents of the belladonna series, is intertwined with the history of morphine. In 1889, Korff first described the use of morphine combined with scopolamine for "twilight sleep." Scopolamine itself does not alleviate pain; morphine relieves the pain, while scopolamine combats certain side effects of morphine. In 1902, twilight sleep was first used in childbirth, and initial reports seemed to indicate that the pain of child-bearing was at last reliably overcome. It was soon extensively employed; but disquieting reports began to accumulate. In many instances, labor was prolonged by the use of these drugs, and infant mortality was on the rise. Nearly as rapidly as it had been accepted, twilight sleep was abandoned. In 1921, there was a revival of interest in twilight sleep, but it was soon shown that increased infant mortality had not been eliminated. Twilight sleep was then again abandoned. Large doses of morphine-scopolamine have been used intermittently as a general anesthetic in surgical cases, but, by and large, the conventional inhalation anesthetics have superseded morphine-scopolamine.

The Hemp Plant

The hemp plant, *Cannabis sativa* (Moraceae) originated in some part of temperate Asia, where the earliest records that we have of it mention its use in medicine. As early as 1000 B.C., the Indian Susruta mentions "bhanga" as a remedy, and the character of the names by which it was designated in early Hindu literature indicates that it was employed for its euphoric properties. The biography of the Chinese physician Hoa-tho (about A.D. 220) mentioned "Ma-Yo," a hemp preparation which induced insensibility before amputation.

The fact that the ancients used a plant medicinally, however, is not a measure of its usefulness today. Analysis of the dried flowers or of the gum resin from wounds made on the stem and branches has shown the active ingredient to be cannabinol. The concentration of cannabinol varies greatly from plant to plant, even among those grown in the same area under virtually identical conditions. For this reason, it has been difficult to prepare standard extracts of the drug. Furthermore, the efficacy of the anesthetic effects of the drug has been questioned. Ethnologic and anthropologic reports from India are rich in references to the use of the smoke from the burned leaves for relieving

pain,[3] and hemp smokers occasionally report a deadened sense of pain as well as the usual distortion of time perception and loss of motor control.

A survey of medical literature indicates that very little research, if any, is currently being carried out on the drug, and several medical and pharmaceutical authorities indicate that it is no longer used in modern medicine, the reasons being its variability, the tendency of the drug to deteriorate and differences in individual susceptibility to its action. Cannabinol, nevertheless, can and does have an analgesic action. It has merely been abandoned for more reliable drugs. In 1930, it was stated in the *Journal of the American Medical Association* (**94**: 165) that

> "The sensation of pain is distinctly lessened or entirely absent and the sense of touch is less acute than normally. Hence a woman in labor may have a more or less painless labor. If a sufficient amount of the drug is taken, the patient may fall into a tranquil sleep from which she will awaken refreshed. . . . As far as is known, a baby born of a mother intoxicated with cannabis will not be abnormal in any way."

The Coca Plant

The last of the major botanical pain relievers is cocaine, an alkaloid obtained from the coca plant, *Erythroxylon Coca* (Erythroxylaceae). A shrub native to the Andes of Peru and unknown in Europe until the conquest of Peru, *E. Coca* was almost indispensable to the Indians; they would not work without a daily allotment of coca. The Spaniards did not adopt the native habit of chewing coca leaves. They considered it an idle indulgence, or worse, a nefarious tool of the devil to keep the Indians from the faith that Spain had brought them. But as soon as the Spaniards realized that the Indians ate less if they were given coca leaves, they quickly reversed their decision and allowed the Indians this indulgence—after putting a tax on the coca plant. We now know that the cocaine in the leaves paralyzes all sensory nerves, and is, therefore, a local anesthetic. It paralyzed the natives' nerves that convey hunger pangs, thereby allowing the natives to work without experiencing the usual discomforts of hunger.

It is the leaves that yield the alkaloid, cocaine. In the Huanaco or Bolivian coca, the leaves are short, greenish brown and petiolate. Native pickers gather the coca leaves in two harvests: usually in April and September. The leaves are dried in the sun, packed in sacks for local transport, and then transferred to metal containers for shipment abroad. By far the greatest amount of the drug is still consumed by the natives in their ancient custom of coca-chewing.

Because the coca-chewing habit dates from the beginning of recorded history in Peru and since the coca leaf can alleviate hunger pangs, students of medical history, anthropologists, and others have long wondered whether the pre-Incan and Incan civilizations used the coca leaf to relieve pain. It is by no means certain that the Incas or pre-Incas even knew of the anesthetic action of coca; but, there is some circumstantial evidence that has led anthropologists and pathologists to this conclusion. First, it is common practice today for the natives to place coca leaves in a wound before attempting any incisions in the general area. Whether this custom arose under the Incan civilization or whether it arose much later is not known; it may, however, be significant. Secondly, we know that the Incas were among the most advanced primitives in surgery. They have left behind surgical instruments, and their graves yield so many trephined skulls (nearly 5% of all skulls are trephined, some in as many as four different places, representing presumably four separate operations) that it is difficult to believe that such extensive surgery could have been done without an anesthetic. On the other hand, we know that in some areas (e.g., Algeria) trephining was done without anesthesia. Even if the Incas did employ anesthesia, they may have had recourse to alcoholic beverages to induce senselessness.

The third reason proposed—the incidence with which trephined skulls were buried with

[3] Normally, the effect is produced by having the sufferer smoke cigarettes or sit in a closed room where the plant is added to fire. But one account tells of an Indian physician who introduced smoke into the patient's anus to ease a colonic spasm of the largest intentine.

little sacks containing coca leaves—can also be disputed. Sacks of coca leaves were buried likewise with bodies with intact skulls. Perhaps a supply of coca was provided for use in after life. Until more precise records and evidence are found, the use of coca leaves as an anesthetic by the Incas will remain supposition, not fact.

That the natives failed to perceive the anesthetic value of coca extract does not imply that the "advanced" European was any more perspicacious. No matter which anesthetic or analgesic plant we consider, we see man's failure to grasp its significance, despite the great need for pain-relievers. The first scientific knowledge of the coca plant in Europe occurs in the writings of a physician of Seville, Nicholas Monardes, in 1565. His "Joyful Newes Out of the Newe Founde Worlde" consisted mainly of an enumeration and description of natural history of the Western Hemisphere. Among the plants described was *Erythroxylon Coca.* The first recorded medical use of coca in Europe was written by Father Blas Valera in 1609. The coca leaf was said to "preserve the body of many infirmities"; unfortunately, this vague description does not tell us whether the coca leaf was used for its anesthetic value or whether it was thought to possess therapeutic properties.

In 1735, Joseph de Jussieu, a member of La Condamine's expedition to South America, sent several specimens of coca to his brother, Antoine, in Paris, where they were preserved in the Museum of Natural History and became the standards for reference. The 18th century saw new attention turned towards the coca plant. Unfortunately, much of the material written about the plant was pseudo-medical, merely reiterating the presumed value of coca infusion as an elixir and tonic. These claims obscured the really important investigations, for when accurate scientific work was done, there was hesitation in accepting it because of the quackery already associated with the plant.

A truly important work on coca was a thesis by Albert Nieman, working under the auspices of the German chemist, Friedrich Wohler. Nieman isolated cocaine. Then placing cocaine crystals on his tongue, he discovered that they anesthetized it. Five years later, in 1864, Dr. Fauvil of Paris employed coca extract locally on the larynx. Dr. Morrell Mackenzie of England and Dr. Louis Eilsberg of the United States both had seen Fauvil operate with this anesthetic, and they introduced the anesthetic use of cocaine into their respective countries. There then occurred one of the most absurd periods in the history of anesthesia—that is the best way to describe it! Strangely enough, no general use was made of cocaine as an anesthetic for nearly a quarter of a century, despite the success experienced by these three eminent physicians.

In 1884, cocaine came to the attention of the Viennese physician, Carl Koller. It has been said that a student of Koller's accidentally applied cocaine to a friend's eye, discovering the resulting anesthesia. Perhaps this story is not entirely credible; nonetheless, Koller reported his success in painless eye-surgery to the German Ophthalmological Congress in 1884. His paper was hardly published when W. S. Halsted and R. J. Hall originated the principle of "nerve blocking." Then, in 1885, J. L. Corning of New York experimented with spinal anesthesia by giving cocaine hydrochloride to dogs and then to human beings. In 1892, Schleish demonstrated infiltration anesthesia by intracutaneous injection, and the various techniques of "local anesthesia" were well launched.

The techniques elaborated with the use of cocaine have persisted; the use of cocaine has not. Though undeniably effective in combatting pain, cocaine has several serious shortcomings. Its anesthetic index is low, not because of low potency but because of high toxicity. Its effects wear off rapidly, requiring repeated injections. Cocaine has undesirable irritant effects in addition to its toxicity. Finally, it cannot be sterilized, for boiling breaks down cocaine. In 1904, Alfred Einhorn synthesized a substance—novocaine—lacking these drawbacks. Many similar compounds followed in rapid succession, and these synthetics have gradually replaced cocaine. But the place of cocaine in the history of relief from pain will always be great.

Miscellaneous Plants

This section comprises a heterogeneous grouping of plants. 1) Some, though decidedly anesthetic, are little used. 2) Some,

though not anesthetic, were once employed as anesthetics; brief notes on their past uses are included. 3) Some seem to be worthy of investigation. Included also is a list drawn up from ethnobotanical sources of plants, used by native peoples to relieve pain which have not yet been studied. Though by no means complete, the list seems worth publishing. 4) There are, finally, plants which have no anesthetic action, but which are used in modern surgical procedures to alleviate pain—adjuncts in man's fight against pain.

Curare. Curare has no anesthetic action whatever, but it is used in surgical procedures designed to relieve pain and preserve life. The early accounts of curare arrow-poisons are extremely confused; we know now that the descriptions did not always refer to the same poison. In 1516, Peter Martyr Anghierus described "curare," and in 1595, Sir Walter Raleigh gave an early English account of "curare" in his "Discovery of the Large, Rich, and Beautiful Empire of Guiana."

Schomburgk published *On the Urari* in 1837, reporting his observations on the native method of preparing the poison. The Indians of British Guiana used more than half a dozen poisonous plants. Schomburgk judged the principal poison to be the bark of *Strychnos toxifera*. This contributed to the belief that "curare" was a strychnine-like convulsant poison. Much of the curare of South America—including that which has supplied therapeutically valuable agents—is made principally from various menispermaceous plants, especially of *Chondrodendron*, *Abuta* and several related genera.

The French physiologist, Claude Bernard, began his experiments with curare in 1884. Accurate physiological experiments, however, could not be carried out until the drug had been extracted and purified; the chemists Preyer (1865) and Boehm (1886–1897) are credited with these achievements. But years passed before modern medicine knew definitely the source of the drug and acquired adequate supplies of it.

In 1934, Richard Gill obtained the first good supply of curare of carefully determined botanical origin from Ecuador. Upon his return to this country in 1938, the potentialities of curare were brought to the attention of several physicians. Then, in 1935, Harold King showed that the activity of curare was due principally to the alkaloid l-tubocurarine. E. R. Squibb and Sons began marketing the chloride of the alkaloid under the trade name "Intocostrin" in 1939; it was this product which was first used by physicians in surgery.

Dr. H. Griffith at the Homeopathic Hospital of Montreal first administered Intocostrin to a patient under anesthesia in January, 1942. His success was reported in *Anesthesiology* of July, 1942. The use of curare derivatives as muscle relaxants in surgery subsequently gained wide acceptance. A host of commercial competitors of Intocostrin have been brought out, most of which vary only slightly from Intocostrin in their effect. Griffith, some nine years after his initial experiment, and after trying most of the commercial varieties of curare himself, wrote: "Personally, [I] am quite unable to decide whether any one is safer or better than several others." (35)

Curare derivatives characteristically block transmission of nervous impulses across the neuro-muscular junction to the muscles. Thus, muscle contraction is prevented. With curare relaxation, the surgeon can then give his full attention to operating.

Ololiuqui (*Rivea corymbosa*) is a large, twining, woody vine of the Convolvulaceae; a Morning Glory. Early accounts of the plant were written by the Spanish chroniclers of Mexico shortly after the Conquest. In 1590, Acosta first reported the anesthetic properties of ololiuqui seeds in his *Historia natural y moral de las Indias*. . . He wrote [fide Schultes (73)]:

> "They said they felt thereby a notable ease, which might be, for that the tobacco and ololiuqui have this property of themselves, to benumb the flesh, being applied in manner of an emplaste, which must be by a stronger reason, being mingled with poison, and for that it did appease and benumb the pains, they held it for an effect of health of a divine virtue."

The religious persecution of native cults by the Spaniards forced their rituals into hiding; since ololiuqui seeds were used in these rituals, the botanical identity of the

plant also was lost. Botanists, unable to point to narcotic principles in the family, were left to guesswork. Safford deduced that "ololiuqui" could not be a Convolvulaceae, for no member of this family was known to contain a principle acting on the central nervous system. He suggested that the early accounts described *Datura* flowers, and he noted that the narcosis described by the early writers resembled *Datura*-intoxication. Safford's reasonable deductions were wholly wrong. In 1938, Schultes found *Rivea corymbosa* in use as a narcotic in Oaxaca, Mexico, and advised investigation of the anciently reputed analgesic properties of the seeds (73):

> "The numerous statements to the effect that ololiuqui was used to benumb the flesh and to mitigate pain command attention, because of the fact that an analgesic alkaloid has been isolated from a related convolvulaceous plant—*Convolvulus pseudocantabricus*— . . . it seems very probable that the seeds were used by the Aztecs to kill pain and that further investigation of *Ricea corymbosa* may reveal that this plant . . . possesses analgesic constituents."

Further investigation was not forthcoming. In 1956 (74) and again in 1960, Schultes (75) recommended that investigation be begun. Osmond, a Canadian psychiatrist, had, by this time, reported the experimental effects of the seeds.

What was needed was chemical isolation of the active principle. Finally, in 1960, Hoffman and Tscherter (44) reported the isolation of three crystalline alkaloids of the ergot type from *Rivea corymbosa*: namely, ergine, isoergine, and chanoclavin. It is remarkable that a species in such an advanced family should have alkaloids found also in the fungi. These alkaloids, however, apparently lack analgesic properties. Was the early report inaccurate or is there still investigation to carry out?

The poison hemlock. The poison hemlock (*Conium maculatum*) has been used as a local anesthetic from classical times. It is now known that the fully grown, unripe fruits of the herb contain the toxic ingredients coniine, methylconiine, cicutoxin, conydrine, conic acid, oil of conium and paraconiine. In particular, the alkaloid coniine has been used as a medullary depressant. Apparently the ancients, aware of the poisonous action of coniine when taken internally, supposed that it would be efficacious if used externally as well. Using the poison hemlock as a local anesthetic may have gained them placebo-like relief from pain, but no other relief, since *Conium*-extract is absorbed apparently neither through broken nor unbroken skin. The poison hemlock is not an anesthetic agent; all reports to the contrary are unsound.

Aconite. Aconite is obtained from the tuberous roots of the perennial herb, the monkshood (*Aconitum Napellus*), native to the Alps, Pyrenees, and other mountainous regions of Europe and Asia. Of the 80-odd species of *Aconitum,* many are poisonous. The first mention of the use of aconite as an anesthetic in surgery is found in the early Chinese literature: Hoa-Tho combined aconite (species unknown), Daturas, and Hyoscyamus as an inhalation anesthetic. In ancient Greece, the herb had a reputation like that of the upas-tree (*Antiaris toxicaria*). It was not employed in medicine, however, until 1762, when Störck, a Viennese physician, introduced it into regular practice. The commercial supply of the drug comes chiefly from Europe, and in general, the drug was used more widely there than in the United States. The plant contains several alkaloids, the chief of which is aconitine. Aconitine is a poison when taken internally, a local anesthetic when used externally. But it paralyzes the senses of touch and temperature as well as those of pain, and care must be taken not to use the drug in the area of an open wound, lest the drug enter the circulatory system. These dangerous characteristics have led to its abandonment by medical practitioners. A survey of the current literature reveals no recent work on the drug; it has apparently lapsed into obscurity as newer, better drugs became available.

Gelsemium. Gelsemium is an ornamental evergreen vine, native to the woodlands and lowlands of the American South. The roots of the yellow jasmine or jessamine, as it is commonly known, yield the alkaloid gelsemidine which acts primarily as a stimulant, but, with increasing dosage, as a depressant. Gelsemidine's mode of action is apparently

unknown. Formerly, gelsemidine was used as a sedative and analgesic. It is currently employed in treating certain facial neuralgias.

Duboisia. *Duboisia myoporoides,* a large solanaceous shrub native to northern Australia, has long been used by natives as a masticatory and fumatory: its alkaloids first stimulate, then narcotize. Another species of *Duboisia, D. Hopwoodii,* or "pituri," was similarly used. An additional use was that of a fish poison. Investigation has shown that the active ingredients are hyoscyamine and scopolamine. This shrub is, at present, the chief commercial source of scopolamine.

List of additional plants. In surveying the literature, many plants, other than those discussed above, were noted as possessing pain-relieving properties. These plants are listed below, along with the bibliographical source, and, whenever possible, the purpose for which it was used and the part of the plant employed. Since this is merely a compilation of literature references, it should be taken as an entirely uncritical listing.

TABLE 1. LIST OF PLANTS POSSESSING PAIN-RELIEVING PROPERTIES

Plant	Part Used	To Relieve	Bibliographic Source
Achillea borealis	-------	pain of heat	79
Achillea lanulosa	leaves, root	toothache	83
Achras Zapota	gum	toothache	78
Actaea arguta	roots	rheumatism	20
Azfelia quanzensis	bark	toothache	32
Aloe vera	leaf pulp	headache	78
Aplopappus spinulosus	-------	toothache	89
Anacardium occidentalis	bark, leaves	toothache	21
Antennaria margaritaceum	flowers	-------	46
Anthemis Cotula	-------	-------	46
Arctium Lappa	-------	-------	46
Argemone mexicana	juice	skin pain	33
Aristolochia mexicana	-------	rheumatism	27
Aristolochia serpentaria	-------	-------	46
Artemisia discolor	-------	-------	76
Asclepias syriaca	-------	-------	46
Bixa Orellana	leaves	headache	78
Calophyllum inophyllum	gum	----	22
Castalia odorata	-------	-------	46
Catalpa bignonioides	pods	-------	46
Celtis occidentalis	bark	-------	46
Chlophophora tinctoria	sap	toothache	78
Cicuta maculata	-------	-------	46
Clematis lingusticifolia	-------	-------	89
Corylus americana	nut-oil	toothache	46
Cryptantha Jamesii	-------	earache	89
Cynoglossum officinale	-------	raspy cough	16
Datura innoxia	-------	-------	22
Derris elliptica	whole plant	itches	66
Ervatamia divaricata	root	-------	22
Erythrina suberosa	leaves	toothache	22
Eucalyptus tereticornis	-------	-------	66
Euphorbia gorgonis	latex	toothache	59
Euphorbia hirsuta	-------	-------	46
Faurea speciosa	leaves	earache	32
Ferula Narthex	gum	-------	22
Gazania pinnata	root	toothache	59
Gnaphalium polycephalum	-------	-------	46
Hamamelis virginiana	-------	-------	40
Heckaria umbellata	-------	headache	77
Helenium Hoopesii	root	rheumatism	20
Humulus Lupulus	-------	-------	46
Indigofera tinctoria	leaves	stings	22

TABLE 1.—Continued

Jasminum Sambac	roots	-------	66
Krugiodendron ferreum	bark	toothache	78
Lactuca canadensis	leaves	-------	46
Lactuca elongata	leaves	-------	46
Lycopodium clavatum	-------	headache	76
Malvastrum coccineum	-------	pain of heat	79
Melaleuca leucodendron	-------	general aches	66
Mentha arvensis	-------	headache	66
Mentha piperita	-------	-------	46
Noringa oleifera	-------	-------	22
Ocimum sanctum	roots, leaves	stings, earache	22
Oroxylon indicum	root bark	-------	22
Papaver dubium	-------	-------	46
Peganum Harmala	seed	-------	22
Pimpinella Anisum	seed	rheumatism	20
Plantago cordata	leaves	-------	46
Plumbago capensis	root	headache	59
Psoralea pentaphylla	-------	labor pains	27
Randia dumetorum	bark	rheumatism	22
Sanicula canadensis	root	-------	46
Sanicula marilandica	root	-------	16
Sanseviera thyrsiflora	leaf	toothache, earache	59
Sarracenia variolaris	-------	-------	46
Scopola carniolica	-------	-------	64
Scopola japonica	rhizomes	-------	17
Scrophularia nodosa	-------	-------	16
Semecarpus Anacardium	-------	-------	22
Senecio Balsamitae	-------	-------	46
Solanum carolinense	fruit	-------	46
Solanum Dulcamara	-------	-------	46
Solanum nigrum	berries, leaves	-------	22
Solanum pseudocapsicum	-------	-------	46
Solanum virginianum	leaves	-------	46
Solanum xanthocarpum	leaves	-------	22
Spirostachys africanus	bark	headache	59
Thuja plicata	leaves	general pain	76
Tragia species	-------	surgical pain	26
Ulmus pubescens	-------	-------	40
Urera caracasana	leaves	headache	78
Valeriana pauciflora	root	-------	46
Verbascum blattaria	flowers	-------	46
Verbascum thapsus	root, leaves	earache	46
Verbena ambrosiaefolia	-------	general aches	20
Xanthoxylum fraxineum	-------	toothache	40
Xysmalobium undulatum	root	headache	59
Zea Mays	stigmas	-------	46

Conclusion

The history of the pain-relieving drugs has been an enigma in one respect at least: why, if pain-relieving drugs were so nearly within reach, did it take Man so many centuries to realize their potentialities? Several hypotheses have been put forward. One asserts that doctors were unwilling to experiment, fearing they might inadvertently cause death and thus break the Hippocratic oath. The social scientists sometimes lean to the belief that, because pain provides an opportunity to show fortitude, the demand for pain-relievers may not have been nearly so great as we are now led to assume it to have been. "Union Rules" also come in for their share of "guilt." In medieval times, the physicians' guilds strictly prohibited surgeons from giving internal medicines, for surgeons were considered mere unlettered craftsmen. Thus, they could do little about relieving pain, even if they were inclined to try. Finally, religious-superstitious beliefs can be held

partly responsible. Pain and death were held by many cultures to be inflicted by God on a wicked people, and any attempt to avoid them could be considered opposition to Divine Will.

The future will certainly see no decrease in the demand for pain-relieving drugs. If the present state of affairs can be taken as an indication, the decline in importance of botanical analgesics and anesthetics should continue. Nature has fortuitously provided Man with certain pain-relieving drugs; Man improves on his legacy. With advanced chemical techniques, pharmacologists and chemists are now able to prepare an infinite variety of compounds, delicately balancing their toxic against their therapeutic properties. Man's rational planning has in the end yielded better anodynes than Nature's random gifts. Nature has provided the starting point for chemical research, and Man has learned to attempt variations on Nature's themes. We might well expect Man to continue making superior analgesics and anesthetics—and Nature to go right on providing starting points for his research.

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